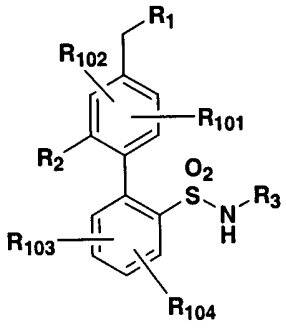
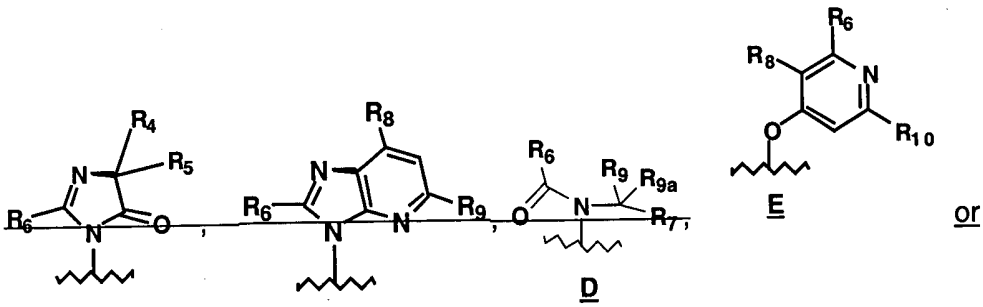
**In Th Claims:**

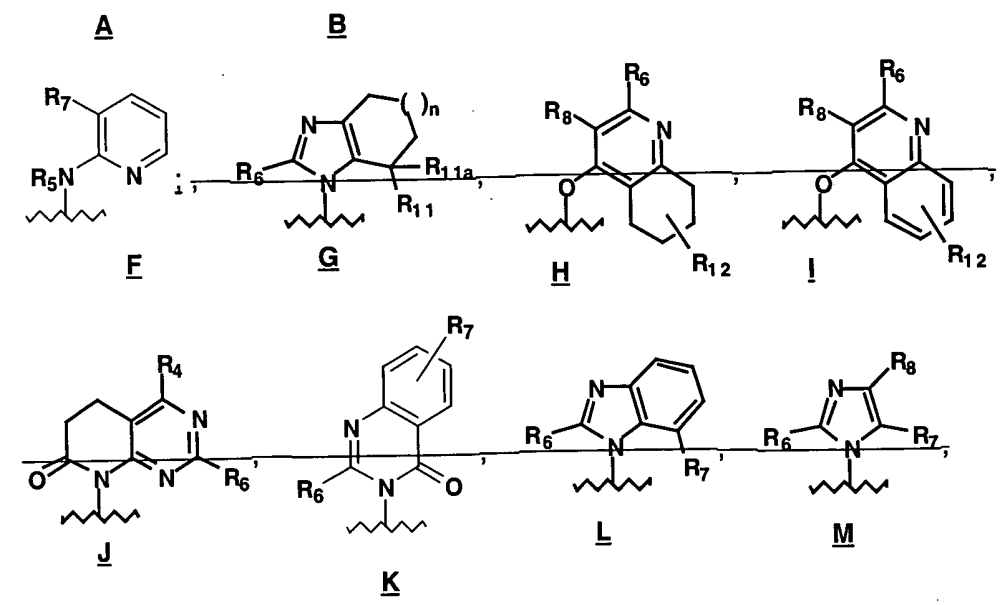
1. (Currently Amended) A compound of the following formula I, ~~or an~~ enantiomers, diastereomers, salts ~~or metabolite~~ and solvates thereof:



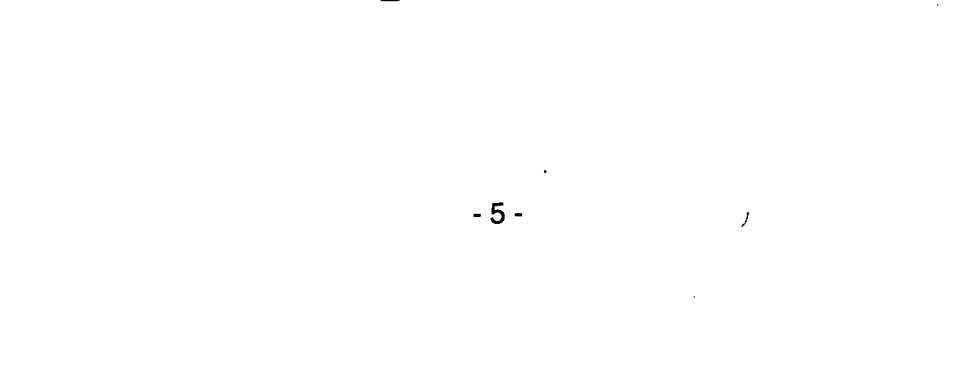
I

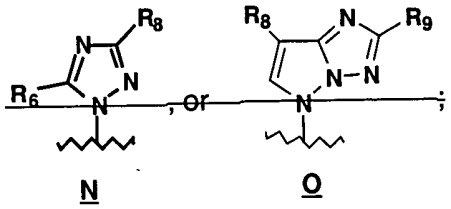
wherein:

$R_1$ is  or









N O

$R_2$ is hydrogen, halogen, -CHO, alkyl, haloalkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, aryloxy alkoxyalkoxy, cyano, hydroxy, hydroxyalkyl, nitro, $-CH(OR_{13})(OR_{14})$, or $-(CH_2)_wY$; ~~with the proviso that when $R_1$ is B, $R_2$ is not hydrogen, halogen, alkyl, haloalkyl, alkoxy, hydroxyalkyl, nitro, $-(CH_2)_wNR_{19}R_{20}$ or $-NHSO_2R_{22}$;~~

$R_3$ is heteroaryl;

~~$R_4$ and~~ $R_5$ ~~are each independently~~ is alkyl, hydroxyalkyl, cycloalkyl, hydroxy substituted cycloalkyl, alkoxyalkyl, or hydroxy substituted alkoxyalkyl; ~~, or $R_4$ and $R_5$ together form a cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl or tetrahydropyranyl ring which may be optionally substituted with one or more hydroxy groups;~~

$R_6$ is alkyl, hydroxyalkyl, haloalkyl, hydroxy substituted haloalkyl, cycloalkyl, hydroxy substituted cycloalkyl, (cycloalkyl)alkyl, hydroxy substituted (cycloalkyl)alkyl, aralkyl, alkoxy, hydroxy substituted alkoxy, alkoxyalkyl, hydroxy substituted alkoxyalkyl, or $-NR_{16}R_{17}$;

$R_7$ is $-(CH_2)_w-CO_2R_{15}$, $-(CH_2)_w-(C=O)NR_{16}R_{17}$, $-(CH_2)_w-NR_{15}(C=O)NR_{16}R_{17}$, $-(CH_2)_w-CH_2OH$, $-(CH_2)_w-(C=O)R_{15}$, tetrazolyl, oxadiazolyl or triazolyl wherein said tetrazolyl, oxadiazolyl or triazolyl may optionally be substituted with hydrogen, alkyl, hydroxy or halogen;

~~$R_8$, $R_9$, $R_{9a}$,~~ and $R_{10}$ ~~and $R_{12}$~~ are each independently hydrogen, halogen, alkyl, hydroxyalkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, heteroaryl, arylalkyl, alkylthioalkyl, alkoxy or alkoxyalkyl; , ~~or $R_9$ and $R_{9a}$ together with the carbon atom to which they are bonded form a cycloalkyl ring;~~

~~$R_{11}$ and $R_{11a}$ are each independently hydrogen, alkoxy, or together form a carbonyl;~~

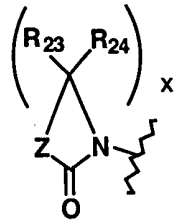
$R_{13}$ and $R_{14}$ are alkyl or together form a five to six-membered ring;

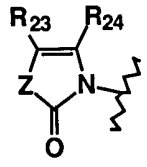
$R_{15}$, $R_{16}$ and $R_{17}$ are independently hydrogen, alkyl, hydroxyalkyl, cycloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, aralkyl, heterocycloalkyl, aryl, heteroaryl or $-(CH_2)_wQ$, or $R_{16}$ and $R_{17}$ may together form a four to six–membered heterocyclic ring;

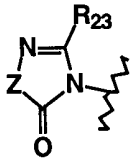
~~n is 1 or 2;~~

w is 0, 1, or 2;

Y is heteroaryl, -COOH, $-COOR_{18}$, $-CONR_{19}R_{20}$, $-NR_{19}R_{20}$, $-NR_{19}-OR_{20}$, $-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)NR_{19}R_{20}$, $-N(R_{19})-(alk)-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)OR_{18}$, $-NR_{21}SO_2R_{22}$, $-SO_2R_{22}$, Q, R or S;

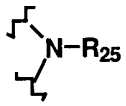
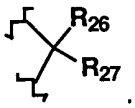
Q is  ;

R is  ;

S is  ;

$R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$ and $R_{22}$ are each independently hydrogen, alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, or $R_{19}$ and $R_{20}$ may together form a four to seven-membered heterocyclic ring;

$R_{23}$ and $R_{24}$ are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

Z is oxygen,  or  ;

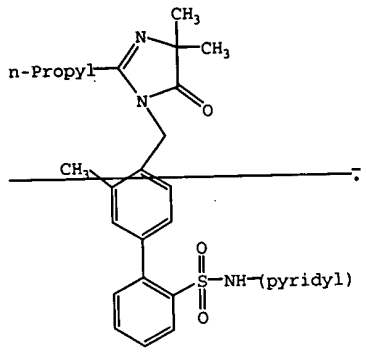
x is 2, 3 or 4;

$R_{25}$, $R_{26}$ and $R_{27}$ are each independently hydrogen, alkyl or cycloalkyl, or $R_{26}$ and $R_{27}$ may together form a three to seven-membered cycloalkyl ring;

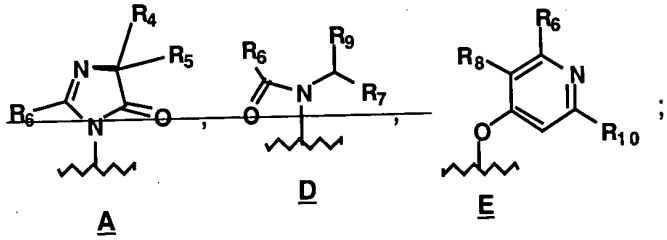
$R_{101}$, $R_{102}$, $R_{103}$, and $R_{104}$ are each independently hydrogen, halogen, -CHO, alkyl, haloalkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, cyano, hydroxy, hydroxyalkyl, nitro, $-CH(OR_{13})(OR_{14})$, or $-(CH_2)_wY$;

wherein said rings; aryl alone or as part of another group; or heteroaryl alone or as part of another group may each optionally be substituted by one or more hydrogen, halogen, cyano, alkyl, hydroxyalkyl, alkoxy, nitro or trifluoromethyl groups; ~~.~~

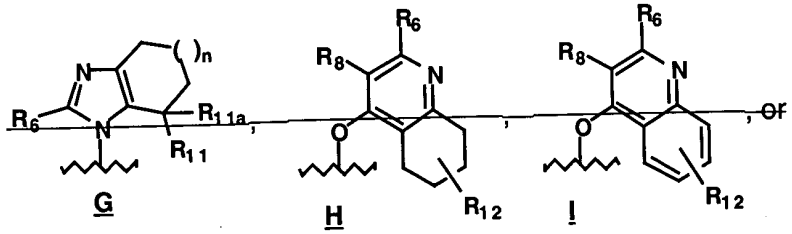
~~provided that when $R_1$ is A said compound is other than~~



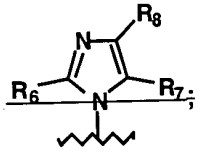

2. (Currently Amended) A compound of claim 1, wherein

$R_1$ is  ;

A D E



G H I



M

$R_2$ is alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or $-(CH_2)_wY$; ~~, or when $R_4$ is D, $R_2$ is hydrogen, alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or $-(CH_2)_wY$;~~

$R_3$ is isoxazolyl pyridizinyl, pyrazinyl or pyrimidinyl, each optionally independently substituted with one to three substituents selected from hydrogen, halogen, cyano, alkyl, alkoxy, trifluoromethyl or nitro;

~~$R_4$ and $R_5$ are each independently alkyl, cycloalkyl , or $R_4$ and $R_5$ together form a cyclobutyl, cyclopentyl or cyclohexyl ring;~~

$R_6$ is alkyl, haloalkyl, cycloalkyl or alkoxy;

~~$R_7$ is $-CO_2R_{15}$, $-(C=O)NR_{16}R_{17}$ or $-CH_2OH$;~~

$R_8$, ~~$R_9$,~~ and $R_{10}$ ~~and $R_{12}$~~ are each independently hydrogen, halogen, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;

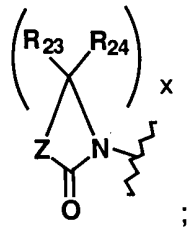
~~$R_{11}$ and $R_{11a}$ are each independently hydrogen, alkoxy, or together form a carbonyl;~~

$R_{15}$, $R_{16}$ and $R_{17}$ are independently hydrogen, alkyl or cycloalkyl or $R_{16}$ and $R_{17}$ may together form a four to six-membered heterocyclic ring;

~~n is 1 or 2;~~

w is 0, 1, or 2;

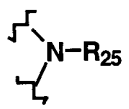
Y is $-COOR_{18}$, $-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)NR_{19}R_{20}$, $-NR_{21}(C=O)OR_{18}$, $-NR_{21}SO_2R_{22}$, $-SO_2R_{22}$ or Q;

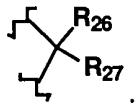
Q is 

;

$R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$ and $R_{22}$ are each independently hydrogen, alkyl, cycloalkyl, or $R_{19}$ and $R_{20}$ may together form a four to seven-membered heterocyclic ring;

$R_{23}$ and $R_{24}$ are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

Z is oxygen, 

or 

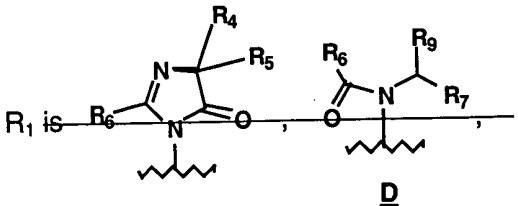
;

x is 2, 3 or 4;

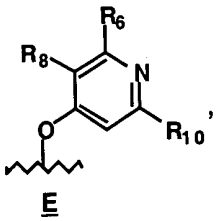
$R_{25}$, $R_{26}$ and $R_{27}$ are each independently hydrogen, alkyl or cycloalkyl, or $R_{26}$ and $R_{27}$ may together form a three to seven-membered cycloalkyl ring;

$R_{101}$, $R_{102}$, $R_{103}$, and $R_{104}$ are each independently hydrogen, halogen, alkoxy or alkyl.

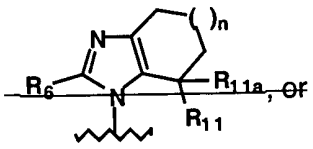
3. (Currently Amended) A compound of claim 1, wherein

$R_1$ is 

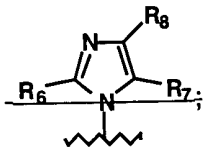
A D



E



G



M

$R_2$ is alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, hydroxyalkyl,or -$(CH_2)_wY$, or when $R_1$ is D, $R_2$ is hydrogen, alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or -$(CH_2)_wY$;

$R_3$ is isoxazolyl, optionally independently substituted with one or two substituents selected from hydrogen, halogen, cyano, alkyl, alkoxy, trifluoromethyl or nitro;

~~$R_4$ and $R_5$ are each independently alkyl, cycloalkyl , or $R_4$ and $R_5$ together form a cyclobutyl, cyclopentyl or cyclohexyl ring;~~

$R_6$ is alkyl, haloalkyl, cycloalkyl or alkoxy;

~~$R_7$ is $-CO_2R_{15}$ or $-(C=O)NR_{16}R_{17}$ ;~~

$R_8$, $R_9$ and $R_{10}$ are each independently hydrogen, halogen, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;

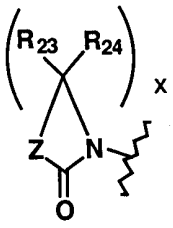
~~$R_{11}$ and $R_{11a}$ together form a carbonyl;~~

$R_{15}$, $R_{16}$ and $R_{17}$ are independently hydrogen, alkyl, or cycloalkyl or $R_{16}$ and $R_{17}$ may together form a four to six-membered heterocyclic ring;

~~n is 2;~~

w is 0, 1, or 2;

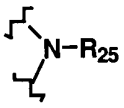
Y is $-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)NR_{19}R_{20}$, $-NR_{21}(C=O)OR_{18}$, $-NR_{21}SO_2R_{22}$, $-SO_2R_{22}$ or Q ;

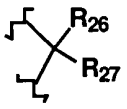
Q is 

;

$R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$ and $R_{22}$ are each independently hydrogen, alkyl, cycloalkyl, or $R_{19}$ and $R_{20}$ may together form a four to seven-membered heterocyclic ring;

$R_{23}$ and $R_{24}$ are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

Z is oxygen, 

or 

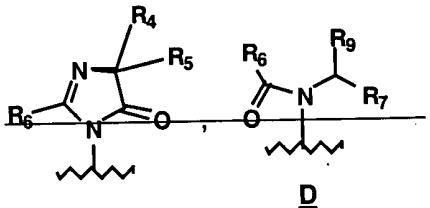
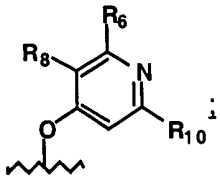
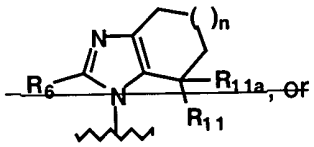
;

x is 2, 3 or 4;

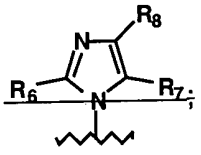
$R_{25}$, $R_{26}$ and $R_{27}$ are each independently hydrogen, alkyl or cycloalkyl, or $R_{26}$ and $R_{27}$ may together form a three to seven-membered cycloalkyl ring;

$R_{101}$, $R_{102}$, $R_{103}$, and $R_{104}$ are each independently hydrogen, halogen, or alkyl.

4. (Currently Amended) A compound of claim 1, wherein

$R_1$ is  ;  ; 

A D E G

 ;

M

$R_2$ is alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl,or $-(CH_2)_wY$; ~~or when $R_1$ is D, $R_2$ is hydrogen, alkyl, haloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkyl, or $-(CH_2)_wY$;~~

$R_3$ is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen;

~~$R_4$ and $R_5$ are each independently alkyl, cycloalkyl, or $R_4$ and $R_5$ together form a cyclobutyl, cyclopentyl or cyclohexyl ring;~~

$R_6$ is alkyl, haloalkyl, cycloalkyl or alkoxy;

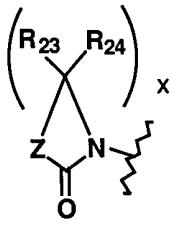
~~$R_7$ is $-(C=O)NR_{16}R_{17}$;~~

~~$R_8$, $R_9$,~~ and $R_{10}$ are independently H, alkyl, cycloalkyl, alkoxy or alkoxyalkyl;

~~n is 2;~~

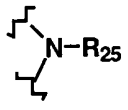
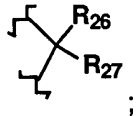
w is 0, 1, or 2;

Y is $-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)NR_{19}R_{20}$, $-NR_{21}(C=O)OR_{18}$, $-NR_{21}SO_2R_{22}$ or Q ;

Q is  ;

$R_{18}$, $R_{19}$, $R_{20}$, $R_{21}$ and $R_{22}$ are each independently hydrogen, alkyl, cycloalkyl, or $R_{19}$ and $R_{20}$ may together form a four-, five-, six- or to seven-membered heterocyclic ring;

$R_{23}$ and $R_{24}$ are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

Z is  or  ;

x is 2;

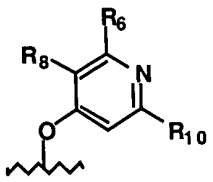
$R_{25}$, $R_{26}$ and $R_{27}$ are each independently hydrogen, alkyl or cycloalkyl, or $R_{26}$ and $R_{27}$ may together form a three-, four-, five, six- or seven-membered cycloalkyl ring;

$R_{101}$, $R_{102}$, $R_{103}$, and $R_{104}$ are each independently hydrogen, halogen, or alkyl.

5. (Original) A compound of claim 1, wherein $R_3$ is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.

6-9. (Cancelled)

10. (Original) A compound of claim 5, wherein $R_1$ is

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11. (Original) A compound of claim 10, wherein $R_2$ is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and $R_{101}$, $R_{102}$, $R_{103}$, $R_{104}$ are each independently hydrogen, halogen, or alkyl.

12. (Original) A compound of claim 10, wherein $R_2$ is $-CH_2Y$.

13. (Original) A compound of claim 12, wherein Y is Q.

14-17. (Cancelled)

18. (Currently Amended) A compound of claim 1, wherein $R_2$ is alkoxyalkyl ~~alkyl~~, haloalkyl or haloalkoxyalkyl .

19. (Original) A compound of claim 18, wherein $R_3$ is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.

20. (Original) A compound of claim 1, wherein $R_2$ is $-CH_2Y$.

21. (Original) A compound of claim 20, wherein $R_3$ is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.

22. (Original) A compound of claim 20, wherein Y is Q.

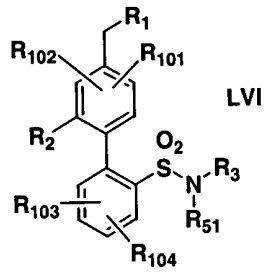
23. (Original) A compound of claim 22, wherein $R_3$ is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.

24-45. (Cancelled)

46. (Original) A pharmaceutical composition for the treatment of an endothelin-dependent or angiotensin II-dependent disorder, comprising a pharmaceutically acceptable vehicle or diluent and at least one compound of claim 1 in an amount effective therefor.

47-48. (Cancelled)

49. (Original) A compound of the formula

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wherein $R_1$, $R_2$, $R_3$, $R_{101}$, $R_{102}$, $R_{103}$, and $R_{104}$ are as defined in claim 1; and
$R_{51}$ is a suitable nitrogen protecting group.

50. (Original) The compound of claim 49, wherein $R_{51}$ is $-CH_2OCH_2CH_2OCH_3$, $-CH_2OCH_2CH_2Si(CH_3)_3$, $-CH_2OCH_3$, or $-CH_2OCH_2$-aryl.

51-64. (Cancelled)

65. (Original) N-(4,5-Dimethyl-3-isoxazolyl)-2'-ethoxymethyl-4'-[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl] [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer or diasteriomer thereof.

66. (Original) N-(4,5-Dimethyl-3-isoxazolyl)-2'-[(2-fluoroethoxy)methyl]-4'-[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl] [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer or diasteriomer thereof.

67. (Original) N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer or diasteriomer thereof.

68-92. (Cancelled)

93. (Original) The pharmaceutical composition of claim 46 further comprising at least one ACE inhibitor.

94. (Original) The pharmaceutical composition of claim 93 wherein said ACE inhibitor is selected from captopril, zofenopril, fosinopril, ceranapril, alacepril, enalapril, delapril, pentopril, quinapril, ramipril, or lisinopril.

95. (Original) The pharmaceutical composition of claim 46 further comprising at least one vasopepsidase inhibitor.

96. (Original) The pharmaceutical composition of claim 95 wherein said vasopepsidase inhibitor is selected from omapatrilat or gemopatrilat.

97. (Original) The pharmaceutical composition of claim 46 further comprising at least one HMG CoA reductase inhibitor.

98. (Original) The pharmaceutical composition of claim 97 wherein said HMG CoA reductase inhibitor is selected from pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 or ZD-4522.

99. (Original) The pharmaceutical composition of claim 46 further comprising at least one anti-platelet agent.

100. (Original) The pharmaceutical composition of claim 99 wherein said anti-platelet agent is selected from clopidigrel, ticlopidine, CS-747 or aspirin.

101. (Original) The pharmaceutical composition of claim 46 further comprising at least one anti-diabetic agent.

102. (Original) The pharmaceutical composition of claim 101 wherein said anti-diabetic agent is selected from biguanides or biguanide/glyburide combinations.

103. (Original) The pharmaceutical composition of claim 46 further comprising at least one beta-adrenergic agent.

104. (Original) The pharmaceutical composition of claim 103 wherein said beta-adrenergic agent is selected from carvedilol or metoprolol.

105. (Original) The pharmaceutical composition of claim 46 further comprising at least one mineralocorticoid receptor antagonist.

106. (Original) The pharmaceutical composition of claim 105 wherein said mineralocorticoid receptor antagonist is selected from spironolactone or eplerenone.

107-108. (Cancelled)